



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C08B 37/16, A61K 31/415, 47/40	A1	(11) International Publication Number: WO 93/13138
		(43) International Publication Date: 8 July 1993 (08.07.93)
(21) International Application Number: PCT/KR92/00083 (22) International Filing Date: 30 December 1992 (30.12.92) (30) Priority data: 1991/25847 31 December 1991 (31.12.91) KR (71) Applicant: SUNKYONG INDUSTRIES CO., LTD. [KR/KR]; 600, Jungja-1dong, Jangan-ku, Suwon, Kyungki-do 440-301 (KR). (72) Inventors: MIN, Dong, Sun ; Woosung Yangjai Apt. 112-303, 154-2, Yangjai-dong, Seocho-ku, Seoul 137-130 (KR). UM, Kee, An ; Youngnam Villa 1-301, 571-13 Pajang-dong, Jangan-ku, Suwon, Kyungki-do 440-290 (KR). KIM, Yong, Soo ; 398-7 Pajang-dong, Jangan-ku, Suwon, Kyungki-do 440-290 (KR). PARK, Pyong, Wook ; Yundai Mansion 18-202, Sinsa-dong, Kangnam-ku, Seoul 135-120 (KR).		(74) Agent: HUH, Sang, Hoon; Room 405, Namyong Building, 809-16, Yeoksam-dong, Kangnam-ku, Seoul 135-707 (KR). (81) Designated States: BR, CA, HU, JP, RU, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: A METHOD FOR PREPARING ENTERIC-COATED ORAL DRUGS CONTAINING ACID-UNSTABLE COMPOUNDS (57) Abstract The present invention relates to a method for preparing enteric-coated oral drugs containing acid-unstable compound, in particular an enteric-coated oral drug prepared in the form of acid-stable dosage units as inclusion complex formed by reacting benzimidazole derivative, acid-unstable compound, with cyclodextrin in alkaline solution.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LJ	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TG	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	ML	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam
FI	Finland				

A METHOD FOR PREPARING ENTERIC-COATED ORAL DRUGS CONTAINING ACID-UNSTABLE COMPOUNDS

BACKGROUND OF THE INVENTION

5 The present invention relates to a method for preparing enteric-coated oral drugs containing acid-unstable compounds, in particular an enteric-coated oral drug prepared in the form of acid-stable dosage units as inclusion complex formed by reacting benzimidazole derivative, acid-unstable compound, with cyclodextrin in alkaline solution.

10 Acid-unstable compounds, especially the benzimidazole compounds, are easily discolored and degraded under acidic and neutral conditions. For example, omeprazole, a benzimidazole derivative, has half-life of 10 minutes in medium of below pH 4, but 18 hours at pH 6.8 and about 300 days at pH 11. Omeprazole has been reported to be stable in alkaline condition [Pilbrant Å and Cederberg C. Scand. J. 15 Gastroenterology, Suppl. 108, 113-120(1985)]. The acid-unstable compounds when exposed to the environment also get discolored and degraded by getting in contact with moisture and organic solvents.

Therapeutic use of the acid-unstable compounds which inhibit gastric acid secretion and are used to cure peptic ulcer and/or duodenal ulcer, requires appropriate 20 mechanism to protect these compounds from degradation in gastric juice after oral administration.

Methods for stabilizing the acid-unstable compound, in particular omeprazole has been known to be as follows ; Omeprazole is combined with alkaline salt such as Na^+ , K^+ , Mg^{+2} , Ca^{+2} and so on to maintain the stability for compound itself. PCT 25 Publication No. 86-00913(PCT/EP 85/00371) discloses to form a stable complex by mixing and reacting omeprazole with β -cyclodextrin in 96% ethanol and cooling the reactant.

The latter process seems to have the problem as the reaction is conducted at a temperature 25 ~ 38°C for 15 hours in ethanol, during the reaction itself omeprazole 30 can get discolored and degraded. Furthermore, it is difficult to expect the formation

of inclusion compound because both omeprazole and cyclodextrin are dispersed in the reaction as solid particles, not dissolved. For forming an inclusion compound of cyclodextrin, the reaction must be carried out in presence of water molecules [K. Hara, H. Hashimoto, J. Jpn. Soc. Starch. Sci., 32(2) 152-161(1986)]. Therefore, the latter method not expected to give inclusion compound since the above reacting condition has not been considered.

On the other hand, Unexamined Korean Patent No. 87-9718 and Korean Patent Publication No. 91-4579 disclose processes for preparing omeprazole preparation consisting of mixing omeprazole with alkaline substance to form core material, forming a watersoluble internal layer on the core and forming an enteric coating to stabilize omeprazole.

It has, however, been found that the stabilizing methods known in the Korean Patents have several problems as followings ; The process for preparing core material and forming enteric-coating is very complicated. The stabilized omeprazole is discolored and degraded during stay in stomach after oral administration, because gastric juice passes through the enteric-coating to partially dissolve the watersoluble internal layer and then infiltrated into the core to dissolve the alkaline substance partially destroying the enteric-coating. The stability of omeprazole by this process is not secured concretely. For formulating omeprazole, it is necessary to give good attention to omeprazole itself. For example, it must be kept at below -20℃ of low temperature and immediately used for formulating after removing moisture, or immediately after synthesis, to maintain the starting stability.

After all, for stabilizing the acid-unstable compound a primary factor is not only to secure the stability of preparation but also to stabilize the compound itself. Thus the attempt to stabilize acid-unstable compound must take into account the stability of the compound during the stabilization process, its stability against gastric juice and the need to quickly and completely dissolve are made the available main drug for absorption in the intestine.

As discussed above most of the previously described methods are either very partially successful in stabilization or the stable inclusion compound is not produced at

all conjugation attempt to add alkaline salt to omeprazole have also been unsatisfactory.

SUMMARY OF THE INVENTION

The object of the present invention is to obtain oral drugs of acid-unstable compound, having excellent storage stability, dissolution and absorption properties after oral administration and a simplified manufacturing process principally involving formation of inclusion complex by reacting the acid-unstable compound with cyclodextrin to give stabilized compound.

The present invention is a method for preparing enteric-coated oral drugs by using cyclodextrin to stabilize acid-unstable compound, characterized in which acid-unstable compound is reacted with cyclodextrin of 1 ~ 10 mole based on 1mole of acid-unstable compound in an alkaline solution to obtain inclusion complex without existence of alkaline substance.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is accomplished by using a new solution system, instead of organic solvent such as ethanol used in prior art, in which acid-unstable compound is reacted with cyclodextrin for stabilizing. The alkaline solution used in the present invention performs a different function from alkaline solvent in prior art. As a result the inclusion complex obtained by the present invention dose not include the alkaline components.

According to the present invention when acid-unstable compound is reacted with cyclodextrin in alkaline solution, the reaction is carried out under homogeneous solution system for 1 ~ 30 mins at 40 ~ 70℃, and after cooling to room temperature the reacted solution is allowed to stand at 4℃ to deposit inclusion complex. The reactant is filtered to remove residual alkaline component and to obtain pured stable inclusion complex as the desired product.

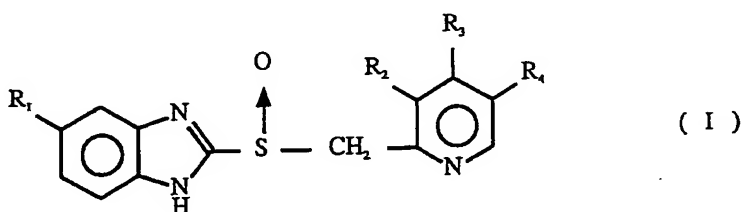
In the above reaction, if the temperature is below 40℃, since the solubility of cyclodextrin is decreased and an excessive of alkaline solution is needed, the reation scale becomes unnecessarily large and the yield is decreased, and if the reaction

temperature is more than 70°C, acid-unstable compound may be discolored or degraded.

Furthermore, under the condition if the reaction time is below 1 min, acid-unstable compound and cyclodextrin not are entirely dissolved in the alkaline solution,
 5 and if the reaction time over 30 mins, acid-unstable compound is also discolored and degraded.

In the present invention, benzimidazole derivative having the following structural formula(I) and pharmaceutically acceptable salt thereof, especially omeprazole and its sodium salt, is preferably used as acid-unstable compound.

10



Wherein,

R₁ is selected from the group consisting of hydrogen atom, methoxy, trifluoromethyl and tetrafluoroethoxy group ;

15 R₂ is selected from the group consisting of hydrogen atom, methylamine and dimethylamine group ;

R₃ is selected from the group consisting of hydrogen atom, methoxy, aryloxy and propaziloxy group ; and

R₄ is hydrogen atom or methyl group.

20 A pharmaceutical preparation containing said acid-unstable compounds in pharmaceutically effective amount may be prepared by the present invention in form of dosage units for oral administration such as tablets, granules, capsules, spherical pellets, microgranules, or microcapsules.

According to the present invention, acid-unstable compound is reacted with
 25 cyclodextrin structurally having hydrophobic cavity of a defined size, and at this time an inclusion complex is obtained because of the property of cyclodextrin to protect hydrophobic compounds from outside by entrapping them into the cavity.

Cyclodextrin may be prepared by resolving starch with cyclodextrin glycosyltransferase and are classified according to the properties and size shown as following Table A.

In accordance with the present invention, a cyclodextrin(CD) selected from the group consisting of α -, β - and γ -cyclodextrin, and cyclodextrin derivatives such as methyl-
 5 β -cyclodextrin, hydroxyethyl β -cyclodextrin, hydroxypropyl α -cyclodextrin, hydroxypropyl β -cyclodextrin, hydroxypropyl γ -cyclodextrin, etc. may be used.

Table A. Comparison of Properties for Natural Cyclodextrins

10	Properties	α -CD	β -CD	γ -CD
	A Number of Glucose Units	6	7	8
	Molecular Weight	973	1135	1297
	Solubility in 25 °C Water (g/100ml)	14.5	1.85	23.2
15	Cavity Diameter (Å)	4.7-5.3	6.0-6.5	7.5-8.3
	Ring-opening Half-life (h) *	6.2	5.4	3.0

* (Note) Ring-opening half-life was measured under the condition of 60 °C, 1N HCl.

20 In the present invention, to obtain stable inclusion complex powder, the used alkaline solution is a aqueous solution of one selected from the group consisting of hydroxides of alkaline metal, alkaline salts of organic or inorganic acid, amines, buffers and combinations thereof.

The alkaline compounds in the present invention as alkaline aqueous solution
 25 may be typically illustrated as followings : Hydroxide of alkaline metal may be selected from the group consisting of sodium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide and combinations thereof. Alkaline salt may be selected from the group consisting of sodium borate, sodium carbonate, sodium phosphate, potassium borate, potassium carbonate, potassium phosphate, sodium
 30 acetate, sodium citrate and combinations thereof. Amines may be selected from the

group consisting of diethylamine, triethylamine, butylamine, ethylenediamine, triethanolamine, propylamine, dipropylamine, diethanolamine, monoethanolamine, isobutylamine, diisopropylamine, tert-butylamine, dibutylamine, diisobutylamine, tributylamine, pentylamine, dipentylamine and combinations thereof. Buffer
5 solution may be selected from the group consisting of carbonate buffer, phosphate buffer, borate buffer, amine salt buffer and combinations thereof.

When the aqueous solution of hydroxide of alkaline metal, alkaline salt of organic or inorganic acid, or buffer solution are used as alkaline solution, the lower pH of alkaline solution affects the acid-unstable compound which may be discolored or
10 degraded during stabilizing reaction. Also, the higher pH of the reaction solution requires longer water-washing time to obtain neutral inclusion complex of acid-unstable compound included in cyclodextrin and the yield is decreased due to partially washing out the inclusion complex during the water-washing. Therefore, alkaline solution may be preferably used between pH 8.0 and 12.0.

15 In the case of independently using amine in alkaline solution, an amine water solution of 0.01 ~ 0.5M may be preferably used to form inclusion complex under stable condition and to reduce after-treatment time.

On the other hand, the above cyclodextrin in the present invention is preferably used in a ratio of 1 ~ 10 mole based on 1 mole of acid-unstable compound. If the
20 used amount of cyclodextrin is below 1.0 mole, unincorporated acid-unstable compound is remain in excess of quantity, and if over 10 mole, the amount of acid-unstable compound in the obtained inclusion complex is decreased by existence of unreacted cyclodextrins.

In accordance with the present invention the clear solution obtained by the
25 above reaction is cooled to low temperature(4°C) and maintained for 3 ~ 15 hours at that temperature to afford the desired inclusion complex formation as microcrystalline powder. The cooling of reaction mixture to give inclusion complex must be very carefully observed to see how the crystalline deposit is formed. If the treating time is below 3hours, inclusion complex is not sufficiently deposited, and if over 15 hours,
30 the productivity of desired product is decreased and the inclusion complex may be

discolored in the reacted solution.

The obtained inclusion complex is washed with some cooled-water several times to completely remove the remaining alkaline component on the inclusion complex, and then the refined complex of neutrality is obtained. Otherwise, the reacted solution may be purified by spray drying, freeze drying, vacuum evaporating or recrystalline method to obtain a refined inclusion complex power as stable compound, and at this time the refining process may be carried out as per prior art according to properties of solution system, namely kind of solution.

The above inclusion complex obtained by the present invention is to obviously improve storage stability of compound itself, and simultaneously to entirely maintain the stability during formulating process and in gastric juice with excellent dissolution and absorption properties. In the stabilized inclusion complex, there is no alkaline component, because the alkaline solution according to the present invention was only used as reacting solution in the stabilizing process. This process is different in the used art and objective because the core material obtained is free from alkali component common with prior art.

In the formulation of pharmaceutical preparation containing the inclusion complex of the present invention in the form of dosage units for oral administration, the above inclusion complex may be mixed with excipients such as microcrystalline cellulose, starch, manitol, etc., disintegrants such as sodium starch glycolate, etc. and lubricants such as magnesium stearate. The mixture is then pressed into tablets including active component, for example omeprazole of 20mg per tablet. The prepared tablets may be coated with a watersoluble substance selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylidone and polyvinylalcohol, and thereafter coated with an enteric-coating agent selected from the group consisting of hydroxypropylmethyl cellulose phthalate, celluloseacetate phthalate and metacrylic acid-methyl metacrylate copolymer, which is mixed with plasticizer in organic solvent.

The enteric-coated oral drugs formulated according to the present invention may be, as stabilized preparation including acid-unstable compound as active component,

therapeutically administrated for the treatment of gastrointestinal disorders. The process described herein is successful in improving stability of acid-unstable compounds against acid, improves dissolution properties and improve preservability.

Especially in case of omeprazole, this process entirely resolves the problems related to stability.

The followings illustrate a preferred embodiment of the present invention without being limited thereto.

Preparing Example 1 : Buffer Solution(Phosphate)

10

To prepare an alkaline solution for stabilizing acid-unstable compound, 0.1M NaOH was added in 500ml of 0.1M KH_2PO_4 as following Table 1.

Those solutions were diluted with water to obtain phosphate buffer solutions of each 1000ml. Each pH of the resulted buffer solutions was measured to be selectively used for an alkaline solution.

Table 1.

	Preparing Ex. 1	0.1M NaOH (ml)	pH
20	1 - 1	224	6.8
	1 - 2	291	7.0
	1 - 3	347	7.2
	1 - 4	391	7.4
25	1 - 5	428	7.6
	1 - 6	453	7.8
	1 - 7	467	8.0

Preparing Example 2 : Buffer Solution(Borate)

0.1M NaOH was added in 500ml of 0.1M H₃BO₃-KCl to obtain borate buffer solutions according to the above Preparing Example 1 as following Table 2. Each pH of the resulted buffer solutions was measured to be selectively used for an alkaline solution.

10 Table 2.

	Preparing Ex. 2	0.1M NaOH (ml)	pH
	2 - 1	39	8.0
15	2 - 2	60	8.2
	2 - 3	86	8.4
	2 - 4	118	8.6
	2 - 5	158	8.8
	2 - 6	208	9.0
20	2 - 7	264	9.2
	2 - 8	321	9.4
	2 - 9	369	9.6
	2 - 10	406	9.8
	2 - 11	437	10.0
25	2 - 12	462	10.2

Preparing Example 3 : Tris Buffer Solution

0.1M HCl was added in 500ml of 0.1M tris(hydroxymethyl) amino methane to
5 obtain amine salt buffer solutions according to the above Preparing Example 1 as
following Table 3. Each pH of the resulted buffer solutions was measured to be
selectively used for an alkaline solution.

10 Table 3.

	Preparing Ex. 3	0.1MHCl (ml)	pH
	3 - 1	466	7.0
15	3 - 2	447	7.2
	3 - 3	420	7.4
	3 - 4	385	7.6
	3 - 5	345	7.8
	3 - 6	292	8.0
20	3 - 7	229	8.2
	3 - 8	172	8.4
	3 - 9	124	8.6
	3 - 10	85	8.8
25	3 - 11	57	9.0

Preparing Example 4 : Buffer Solution (Borate)

0.1M HCl was added in 500ml of 0.025M $\text{Na}_2\text{B}_4\text{O}_7$ to obtain borate buffer solutions according to the above Preparing Example 1 as following Table 4. Each pH of the resulted buffer solutions was measured to be selectively used for an alkaline solution.

10

Table 4.

	Preparing Ex. 4	0.1M HCl (ml)	pH
15	4 - 1	205	8.0
	4 - 2	188	8.2
	4 - 3	166	8.4
	4 - 4	135	8.6
	4 - 5	94	8.8
20	4 - 6	46	9.0

25

30

Preparing Example 5 : Buffer Solution (Borate)

0.1M NaOH was added in 500ml of 0.025M $\text{Na}_2\text{B}_4\text{O}_7$ to obtain borate buffer solutions according to the above Preparing Example 1 as following Table 5. Each pH of the resulted buffer solutions was measured to be selectively used for an alkaline solution.

10 Table 5.

	Preparing Ex. 5	0.1M NaOH (ml)	pH
	5 - 1	9	9.2
15	5 - 2	62	9.4
	5 - 3	111	9.6
	5 - 4	150	9.8
	5 - 5	183	10.0
	5 - 6	205	10.2
20	5 - 7	221	10.4
	5 - 8	233	10.6
	5 - 9	242.5	10.8

Preparing Example 6 : Buffer Solution (Carbonate)

0.1M NaOH was added in 500ml of 0.05M NaHCO₃ to obtain carbonate buffer solutions according to the above Preparing Example 1 as following Table 6. Each pH of the resulted buffer solutions was measured to be selectively used for an alkaline solution.

Table 6.

	Preparing Ex. 6	0.1M NaOH (ml)	pH
15	6 - 1	50	9.6
	6 - 2	76	9.8
	6 - 3	107	10.0
	6 - 4	138	10.2
	6 - 5	165	10.4
20	6 - 6	191	10.6
	6 - 7	212	10.8
	6 - 8	227	11.0

Preparing Example 7 : Buffer Solution (Phosphate)

0.1M NaOH was added in 500ml of 0.05M Na₂HPO₄ to obtain phosphate buffer solutions according to the above Preparing Example 1 as following Table 7. Each pH of the resulted buffer solutions was measured to be selectively used for an alkaline solution.

Table 7.

	Preparing Ex. 7	0.1M NaOH (ml)	pH
	7 - 1	41	11.0
15	7 - 2	63	11.2
	7 - 3	91	11.4
	7 - 4	135	11.6
	7 - 5	194	11.8
20	7 - 6	269	12.0

Preparing Example 8 : Buffer Solution (Chlorate)

0.2M NaOH was added in 250ml of 0.2M KCl to obtain chlorate buffer solutions according to the above Preparing Example 1 as following Table 8. Each pH of the resulted buffer solutions was measured to be selectively used for an alkaline solution.

Table 8.

Preparing Ex. 8	0.2M NaOH (ml)	pH
8 - 1	60	12.0
8 - 2	102	12.2
8 - 3	162	12.4
8 - 4	256	12.6
8 - 5	412	12.8
8 - 6	660	13.0

The obtained buffer solutions may be preferably used in range of pH 8.0 ~ 12.0 for alkaline solution, and hydroxides of alkaline metal or alkaline salt of organic or inorganic salt may be also used by adjusting to range of pH 8.0 ~ 12.0.

But, it is necessary for amines to define the preferable range of alkaline solution by molarity. According to the present invention, water-soluble or water-miscible amines shown on following Table 9, preferably 0.01 ~ 0.5M amines, may be preferably used, but methylamine, dimethyl amine, trimethylamine, ethylamine, isopropylamine, etc. were excluded from studies because of having low boiling point.

Table 9.

	Amines	b.p. (°C)	pKa
5	Diethylamine	55.5	10.98
	Triethylamine	89 - 90	11.01
	Butylamine	77	10.77
	Ethylenediamine	116 - 117	10.71
10	Triethanolamine	335.4	9.50
	Propylamine	48 - 49	10.57
	Dipropylamine	110	11.0
	Diethanolamine	268.8	8.88
	Monoethanolamine	170.8	9.50
15	Isobutylamine	68 - 69	10.42
	Diisopropylamine	83.5	11.05
	Tert-butylamine	43.6	10.87
	Dibutylamine	159.6	11.31
	Diisobutylamine	136 - 140	10.5
20	Tributylamine	91 - 92 (9mmHg)	10.87
	Pentylamine	104	10.63
	Dipentylamine	91 - 93(14mmHg)	11.18

Example 1

β -Cyclodextrin of 24g was dissolved in each 900ml of buffer solutions according to following Table 10 at 40°C, and 3.4g omeprazole was added in the solution under stirring to react for 15 mins.

The reactant was concentrated to 100ml in vacuum evaporator, and after cooling to room temperature, it was left for 6 hrs in a refrigerator to deposit inclusion complex. The filtered inclusion complex was washed with water several times and dried under reduced pressure to obtain omeprazole-cyclodextrin inclusion complex.

The result of reaction and an amount of the obtained inclusion complex were shown as following Table 10.

Table 10.

Example 1	Buffer solution	pH	Inclusion Complex	
			Color	Amount
1 - A	Preparing Ex. 1-2	7.0	±	24.2
1 - B	Preparing Ex. 2-1	8.0	±	24.9
1 - C	Preparing Ex. 2-6	9.0	-	25.9
1 - D	Preparing Ex. 2-11	10.0	-	26.2
1 - E	Preparing Ex. 6-8	11.0	-	26.0
1 - F	Preparing Ex. 7-6	12.0	-	25.3
1 - G	Preparing Ex. 8-6	13.0	-	24.5

(Note) - : Non discoloration

± : Light-violet color

As the result shown in Table 10, it was found that when pH is low the inclusion complex is discolored to light-violet color, and when pH is high the obtained amount of inclusion complex is decreased due to washing with excess water. Therefore a buffer solution was preferably selected between pH 8.0 and pH 12.0 for an alkaline solution.

5

Example 2

β -Cyclodextrin of 24g was dissolved in each 900ml of buffer solutions(pH 9.0, pH 10.0, pH 11.0) according to following Table 11 at 40°C, and 3.4g omeprazole was added in the solution under stirring to react for 15 mins.

10

The reactant was concentrated to 100ml in vacuum evaporator, and after cooling to room temperature, it was left for 6 hrs in a refrigerator to deposit inclusion complex. The filtered inclusion complex was washed with water several times and dried under reduced pressure to obtain omeprazole-cyclodextrin inclusion complex.

The results of reaction were shown as following Table 11.

15

Table 11.

20	Example 1	Buffer solution	pH	Color of Inclusion Complex	Rate of Inclusion(%)
	2 - A	Preparing Ex. 2-6	9.0	-	89.0
	2 - B	Preparing Ex. 3-11	9.0	-	91.2
	2 - C	Preparing Ex. 4-6	9.0	-	90.1
25	2 - D	Preparing Ex. 2-11	10.0	-	98.6
	2 - E	Preparing Ex. 5-5	10.0	-	99.1
	2 - F	Preparing Ex. 6-3	10.0	-	98.9
	2 - G	Preparing Ex. 6-8	11.0	-	99.2
	2 - H	Preparing Ex. 7-1	11.0	-	98.8

30

(Note) - : Non discoloration

As the result shown in Table 11, it is was found that when pH of buffer solution is the same the effectiveness of inclusion is not influenced by kind of buffer solution, and when it is more than pH 10 the rate of inclusion was higher than 98.6%.

5

Example 3

β -Cyclodextrins according to following Table 12 were respectively dissolved in 900ml of buffer solutions(pH 10.0) prepared by the above Preparing Example 2-11 to add omeprazole, and then the reaction temperature was changed to 40°C , 50°C ,60°C ,and 70°C as the reaction being carried out for 15 mins.

10

The reactant was concentrated to 100ml in vacuum evaporator, and after cooling to room temperature, it was left for 6 hrs in a refrigerator to deposit inclusion complex. The filtered inclusion complex was washed with water on several times and dried under reduced pressure to obtain omeprazole-cyclodextrin inclusion complex.

15 The results of reaction were shown as following Table 12.

Table 12.

20

Example 3	Reaction Temp.(°C)	Amount of β -CD (g)	Amount of Omeprazole(g)	Color of Inclusion complex	Rate of Inclusion(%)
25 3 - A	40	24.0	3.4	-	98.6
3 - B	50	54.0	8.2	-	98.8
3 - C	60	85.0	12.9	-	99.0
3 - D	70	135.0	20.5	-	98.0

30 (Note) - : Non discoloration

β -CD : β -cyclodextrin

Example 4

β -Cyclodextrines according to following Table 13 were respectively dissolved in 900ml of buffer solution(pH 10.0) prepared by the above Preparing Example 2-11 at 50°C , and omeprazole was added in the solution under stirring to react for 15 mins.

The reactant was concentrated to 100ml in vacuum evaporator, and after cooling to room temperature, it was left for 6 hrs in a refrigerator to deposit inclusion complex. The filtered inclusion complex was washed with water on several times and dried under reduced pressure to obtain omeprazole-cyclodextrin inclusion complex.

The results of reaction were shown as following Table 13.

Table 13.

Example 4	Kind of CD	Amount of CD(g)	Amount of Omeprazole(g)	Rate of Inclusion(%)
4 - A	α -CD	4.2	5.9	97.2
4 - B	HP- α -CD	1.8	0.25	98.0
4 - C	β -CD	54.0	8.2	98.8
4 - D	HP- β -CD	1.5	0.17	99.2
4 - E	HE- β -CD	1.95	0.23	99.0
4 - F	M- β -CD	2.4	0.3	98.5
4 - G	γ -CD	7.0	0.74	99.1
4 - H	HP- γ -CD	2.4	0.25	99.0

(Note) CD : Cyclodextrin
 HP : Hydroxypropyl
 HE : Hydroxyethyl
 M : Methyl

Example 5

β -cyclodextrin of 54g was dissolved in each 900ml of 0.1M amine aqueous solutions according to following Table 9 at 50°C, and 8.2g omeprazole was added in
5 the solution under stirring to react for 15 mins.

The reactant was cooled to room temperature and/or concentrated to 100ml in vacuum evaporator, and it was left for 6 hrs in a refrigerator to deposit inclusion complex.

The filtered inclusion complex was washed with water several times and dried
10 under reduced pressure to obtain omeprazole-cyclodextrin inclusion complex. The results of reaction were shown as following Table 14.

15

20

25

30

Table 14.

	Example 5	Kind of Amine	Deposition Method	Rate of Inclusion(%)
5	5 - A	Diethylamine	Cool	89.2
	5 - B	Triethylamine	Cool/Conc.	95.7
	5 - C	Propylamine	Cool	90.3
	5 - D	Dipropylamine	Conc.	98.0
	5 - E	Isobutylamine	Cool	89.7
10	5 - F	Diisopropylamine	Cool/Conc.	92.3
	5 - G	Butylamine	Cool	96.7
	5 - H	Ethylenediamine	Conc.	97.1
	5 - I	Monoethanolamine	Conc.	98.9
	5 - J	Diethanolamine	Conc.	99.1
15	5 - K	Triethanolamine	Conc.	99.1
	5 - L	Tert-butylamine	Cool	89.0
	5 - M	Dibutylamine	Conc.	97.3
	5 - N	Diisobutylamine	Conc.	96.8
	5 - O	Tributylamine	Conc.	98.3
20	5 - P	Pentylamine	Conc.	98.7
	5 - Q	Dipentylamine	Conc.	99.3

(Note) Cool : Cooling to room temperature

25 Conc. : Concentrating in vacuum evaporator

Example 6

According to following Table 15, β -cyclodextrin was dissolved in 900ml water, and on the other hand omeprazole was dissolved in 40% (v/v) triethylamine aqueous solution to obtain 27% solution. The resulted omeprazole solution was dropwise added in cyclodextrin aqueous solution.

The reactant was cooled to room temperature, and left for 6 hrs in a refrigerator to deposit inclusion complex.

The filtered inclusion complex was washed with water several times and dried under reduced pressure to obtain omeprazole-cyclodextrin inclusion complex. The results of reaction were shown as following Table 15.

Table 15.

Example 6	Reaction Temp. (°C)	Amount of β -CD(g)	Amount of Omeprazole (g)	Rate of Inclusion (%)
6 - A	40	24.0	3.4	99.5
6 - B	50	54.0	8.2	99.1
6 - C	60	85.0	12.9	98.1
6 - D	70	135.0	20.5	98.5

Example 7

24g β -cyclodextrin was dissolved in 900ml of pH 12 aqueous solutions of hydroxide of alkaline metals according to following Table 16, and 3.4g omeprazole was
5 added in this solution under stirring to react for 15 mins.

The reactant was concentrated to 100ml in vacuum evaporator, and after cooling to room temperature, it was left for 6 hrs in a refrigerator to deposit inclusion complex.

The filtered inclusion complex was washed with water several times and dried
10 under reduced pressure to obtain omeprazole-cyclodextrin inclusion complex. The results of reaction were shown as following Table 16.

Table 16.

15

Example 7	Kind of Hydroxide	Reaction Temp.(°C)	Amount of β -CD (g)	Amount of Omeprazole(g)	Rate of Inclusion(%)
7 - A	NaOH	40	24.0	3.4	99.3
7 - B	KOH	40	24.0	3.4	99.1
7 - C	Ca(OH) ₂	40	24.0	3.4	98.8
25 7 - D	Ba(OH) ₂	40	24.0	3.4	98.7

30

Example 8

This experiment was conducted in same manner as previous Example 7 except that the other alkaline salt solutions according to following Table 17 were used to
 5 obtain omeprazole-dextrin inclusion complex.

The filtered inclusion complex was washed with water several times and dried under reduced pressure to obtain omeprazole-cyclodextrin inclusion complex. The results of reaction were shown as following Table 17.

10

Table 17.

15	Example 8	Kind of alkaline salts	pH	Reaction	Amount of	Amount of	Rate of
				Temp.(°C)	β -CD (g)	Omeprazole(g)	
20	8 - A	Na ₂ B ₄ O ₇	10.0	40	24.0	3.4	99.2
	8 - B	K ₂ B ₄ O ₇	10.0	40	24.0	3.4	99.3
	8 - C	Na ₂ CO ₃	10.0	40	24.0	3.4	99.8
	8 - D	K ₂ CO ₃	10.0	40	24.0	3.4	99.5
	8 - E	Na ₂ HPO ₄	10.0	40	24.0	3.4	99.1
	8 - F	K ₂ HPO ₄	10.0	40	24.0	3.4	99.3
	8 - G	CH ₃ COONa	8.5	40	24.0	3.4	98.7
	8 - H	Sodium citrate	9.0	40	24.0	3.4	98.5

25

30

[Methods for measuring rate of inclusion]

$$5 \quad \frac{\text{Amount of omeprazole in the obtained inclusion complex (g)}}{\text{Amount of used omeprazole (g)}} \times 100 = \text{Rate of inclusion(\%)}$$

The amount of omeprazole in the obtained inclusion complex was measured by
10 HPLC under following conditions.

- Solvent : pH 9.8 Carbonate buffer solution : ethanol = 80 : 20
- Column : μ -Bondapak C₁₈ 3.9mm (the inside diameter) X 300mm (length)
- Mobile Phase : pH 7.6 Phosphate buffer solution : Acetonitrile = 66 : 34
- Detection Wave-length : 302 nm
- 15 • Injection Volum : 20 μ l
- Flow Rate : 1.0 ml/min

Comparative Example 1

5.67g β -cyclodextrin and 1.73g omeprazole were added in 96% ethanol of 20
20 ml and stirred at 30 ~ 32°C for 15 hrs.

After leaving at 10°C for 3hrs, the reacted solution was filtered, and washed with ethanol of 10°C, dried under reduced pressure to obtain the desired product of reddish brown color. At this time the reactant solution was of purple color.

25 Comparative Example 2

2.0g Omeprazole was well mixed with 2.0g Na₂HPO₄, and the mixed compound was dried under reduced pressure to obtain the stabilized core of omeprazole preparation as a comparative sample.

Comparative Example 3

This test was conducted in process of the above Comparative Example 2 except to use 2.0g omeprazole and 2.0g $\text{Mg}(\text{OH})_2$. The obtained core was used as a
5 comparative sample.

Experimental Example 1 (Storage Stability of Inclusion Complex)

To verify stabilized result for the above Example 1 to 8 and Comparative
10 Example 1 to 3, the change of appearance was surveyed with the passing of time under
40°C, 75% RH of accelerated condition. The results were shown on following Table
18.

Under the above condition, storage stability during 6 months means to secure
stability for 3 years at normal condition. As the result of Table 18, it was confirmed
15 that the cases of Example 1 ~ 8 according to the present invention is obviously showing
higher stability than the cases of Comparative Example 1 ~ 3.

Table 18.

Sample	The Change of Appearance				
	Start	After 1month	After 2months	After 4months	After 6months
5 Example 1-D	-	-	-	-	-
Example 2-B	-	-	-	-	-
Example 2-E	-	-	-	-	-
Example 2-G	-	-	-	-	-
Example 3-A	-	-	-	-	-
10 Example 3-D	-	-	-	-	-
Example 4-A	-	-	-	-	-
Example 4-B	-	-	-	-	-
Example 4-D	-	-	-	-	-
Example 4-E	-	-	-	-	-
15 Example 4-F	-	-	-	-	-
Example 4-G	-	-	-	-	-
Example 4-H	-	-	-	-	-
Example 5-B	-	-	-	-	-
Example 5-I	-	-	-	-	-
20 Example 6-A	-	-	-	-	-
Example 6-D	-	-	-	-	-
Example 7-A	-	-	-	-	-
Example 8-C	-	-	-	-	-
Comp. Ex. 1	+	++	++	++	++
25 Comp. Ex. 2	-	±	+	++	++
Comp. Ex. 3	-	-	±	+	+

(Note) - : Non discoloration

± : Some discoloration

30 + : Discoloration

++ : Deep discoloration

Formulation of Inclusion Complex

To formulate enteric-coated oral drugs, the omeprazole-cyclodextrin inclusion complexes obtained by Example 1 ~ 8 were used as followings.

5 [Preparing of Uncoated Tablets]

According to following Table 19, omeprazole of 20mg was homogeneously mixed with excipients, disintegrants and lubricants, and the mixture was tableted to 230mg per unit by Rotary Tableting Machine.

10

Table 19.

(Unit : mg)

15	Mixed Components	Example No.							
		1-D	2-E	3-B	4-A	5-I	6-B	7-A	8-C
	Inclusion complex	165	165	165	165	165	165	165	165
20	Microcrystalline cellulose	42	40	30	30	23	20	20	20
	Dibasic calcium phosphate Anhydrous	20	15	10	5	-	5	-	-
	Corn starch	-	7	22	27	24.7	20	12.7	-
25	Mannitol	-	-	-	-	-	7.7	15	27.7
	Sodium starch glycolate	-	-	-	-	15	10	15	15
	Magnesium stearate	3.0	3.0	3.0	3.0	2.3	2.3	2.3	2.3

30

In the above, when microcrystalline cellulose and dibasic calcium phosphate anhydrous of an excess of quantity were used, hardness of tablets is excellent but disintegration rate was decreased. Therefore, microcrystalline cellulose of small amount was preferably used, and at that time the used amount of corn starch and/or Mannitol were increased and minimum amount of dibasic calcium phosphate anhydrous was used.

[Coating of Watersoluble Substance]

According to following Table 20, a watersoluble substance was coated on uncoated tablets.

Table 20.

(Unit : mg)

15	Components of Watersoluble Substance	(T ₁)	(T ₂)	(T ₃)	(T ₄)	(T ₅)	(T ₆)	(T ₇)	(T ₈)	(T ₉)
	Hydroxy propylmethyl cellulose	10	9	9	9	9	9	-	-	-
20	Hydroxypropyl cellulose	-	-	-	-	-	-	9	-	-
	Polyvinylpyrrolidone	-	-	-	-	-	-	-	9	-
	Polyvinylalcohol	-	-	-	-	-	-	-	-	9
	Propyleneglycol	-	1	-	-	1	-	-	-	-
	Polyethyleneglycol 600	-	-	1	-	-	1	1	1	1
25	Water	190	190	190	38	38	38	38	38	38
	Ethanol	-	-	-	152	152	152	152	152	152

In the above test, when water was only used as solvent or excessive water was used, dry time in coating pan was prolonged.

Since tablets were observed to stick with each other and rendering the coating surface ununiform, ethanol, preferably 80% ethanol water solution, was used in this process as main solvent.

[Coating of Enteric Substance]

According to following Table 21, an enteric substance was coated on tablets coated with watersoluble substance to obtain the desired enteric-coated oral drug.

Table 21.

Components of Enteric Substance		a	b	c	d	e
15	Hydroxypropylmethyl cellulose phthalate	18.6	-	-	18.6	-
	Cellulose acetate phthalate	-	18.6	-	-	18.6
	Eudragit L100	-	-	18.0	-	-
	Cetylalcohol	1.4	1.4	-	-	-
20	Myvacet 9-40T	-	-	-	1.4	1.4
	Dibutylphthalate	-	-	2.0	-	-
	Acetone	152	190	152	152	190
	Ethylalcohol	228	190	-	228	190
	Isopropylalcohol	-	-	228	-	-

Experimental Example 2 : Property Test for Oral Drugs

The obtained inclusion complexes of Examples were used to formulate enteric-coated oral drugs. To survey the properties for the oral drugs, the watersoluble substance according to the method of Table 20(T₅) was respectively coated on tablets prepared from Example 4-A, 5-I, 6-B, 7-A and 8-C, and there after the enteric substance according to the method of Table 21 "d" was coated on the above tablets.

The formulated oral drugs were compared with control product, Astra's LOSEC, to survey acid-resistance property, dissolution property, and storage stability as followings.

[Test for Acid-resistance Property]

The formulated oral drugs were put into artificial gastric fluid [USP, 1st solution] without enzyme and stirred at 37°C by paddle at 100 rpm.

The test solution was left for 2hrs to survey the change of appearance, and the omeprazole existing in preparation was measured by HPLC. The results were shown on following Table 22.

Table 22.

20	Testing Sample	Amount of the Existing Omeprazole(%)	The Change of Appearance
	Example 4-A	99.0	Non discoloration
	Example 5-I	99.1	"
25	Example 6-B	99.5	"
	Example 7-A	100.0	"
	Example 8-C	99.2	"
	Control (Losec)	96.7	Brown spots in pellets

The above test showed brown spots on 40 ~ 75% of pellets for the control(LOSEC), and it was also found that omeprazole content was decreased.

But, the oral drugs prepared according to examples were not affected in the appearance and omeprazole content was scarcely decreased, thus giving superior characteristics.

[Test for Dissolution Property]

To survey the rate of dissolution in the small intestines, the formulated oral drugs were added to simulated gastric fluid [USP, 37°C, 100 rpm].

After 2hrs, the above drugs were moved to simulate intestinal fluid [USP, dissolution apparatus No. 2, Paddle Method], and then the amount of dissolved omeprazole was determined by the method of HPLC. The results were shown on Table 23.

Table 23.

(Unit : %)

Testing Sample	Rate of Dissolution for Passing Time		
	10 min	20 min	30 min
Example 4 - A	85.9	97.6	99.2
Example 5 - I	98.2	100.0	100.0
Example 6 - B	90.3	98.0	99.5
Example 7 - A	98.5	99.7	100.0
Example 8 - C	98.0	99.2	99.8
Control (Losec)	91.5	92.0	93.5

34

As the result from the above experiment show, the dissolution rate for all samples was good only Example 4-A and 5-I produced using dibasic calcium phosphate anhydrous as excipient showed Somewhat slow dissolution rate in first 10 minutes.

- 5 The rate of dissolution after 20mins and 30mins, testing samples of Examples were obviously higher than the control.

[Test for Storage Stability]

According to the process of Experiment Example 1, the drugs were kept in glass
10 bottle for 6 months under 40°C , 75% RH of accelerated condition and 50°C, 75% RH of harsh condition.

The changes of appearance for the resulted samples were surveyed. The results were shown on Table 24.

Table 24.

15

Testing Sample	Test condition	
	40°C, 75% RH	50°C, 75% RH
Example 4 - A	-	-
Example 5 - I	-	-
Example 6 - B	-	-
Example 7 - A	-	-
25 Example 8 - C	-	-
Control (Losec)	±	++

- (Note) - : Non discoloration
 ± : Some discoloration
 30 + : Discoloration
 ++ : Deep discoloration

35

As the result of above, it was confirmed that the storage stabilities of Examples were obviously higher than the control.

As the result of Experimental Example 2, it was found that the enteric-coated oral drugs of the present invention formulated with omeprazol-cyclodextrin inclusion
5 complex have excellent stability and dissolution property as compared with known preparations.

10

15

20

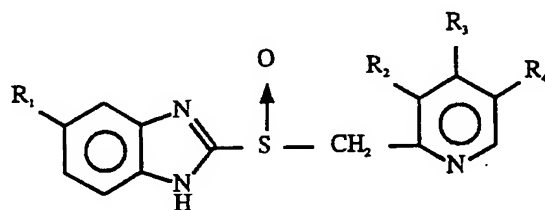
25

30

WHAT IS CLAIMED IS :

1. A method for stabilizing an acid-unstable compound comprising : reacting an acid-unstable compound with a cyclodextrin in an alkaline solution, the ratio of said acid-unstable compound to said cyclodextrin in said reaction being from about 1 : 1 to about 1 : 10.

2. In the method of claim 1, said acid-unstable compound comprising a benzimidazol derivative having the following structural formula, and pharmaceutically acceptable salts thereof,



wherein,

R_1 is selected from the group consisting of hydrogen, methoxy,

trifluoromethyl and tetrafluoroethoxy radicals ;

R_2 is selected from the group consisting of hydrogen, methylamine and dimethylamine radicals ;

R_3 is selected from the group consisting of hydrogen, methoxy, aryloxy and propaziloxy radicals ; and

R_4 is selected from the group consisting of hydrogen and methyl radicals.

3. In the method of claim 1, said acid-unstable compound is omeprazole.

4. In the method of claim 1, said alkaline solution consists essentially of an aqueous solution of an alkali selected from the group consisting of alkaline hydroxides, alkaline salts, amines, buffers, and combinations thereof.

5. In the method of claim 4, said alkaline hydroxide is selected from the group consisting of sodium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide and combinations thereof.
- 5 6. In the method of claim 4, said alkaline salt is selected from the group consisting of sodium borate, sodium carbonate, sodium phosphate, potassium borate, potassium carbonate, potassium phosphate, sodium acetate, sodium citrate and combinations thereof.
- 10 7. In the method of claim 4, said amine is selected from the group consisting of diethylamine, triethylamine, butylamine, ethylenediamine, triethanolamine, propylamine, dipropylamine, diethanolamine, monoethanolamine, isobutylamine, diisopropylamine, tert-butylamine, dibutylamine, diisobutylamine, tributylamine, pentylamine, dipentylamine and combinations thereof.
- 15 8. In the method of claim 4, said buffer is selected from the group consisting of carbonate buffer, phosphate buffer, borate buffer, amine salt buffer, and combinations thereof.
- 20 9. The method of claim 1 further comprising adjusting the heat content of the reaction mixture in a manner effective to maintain the reaction temperature between about 40 and about 70°C.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 92/00083

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁵: C 08 B 37/16, A 61 K 31/415, 47/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁵: C 08 B, A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A1, 86/00 913 (BYK GULDEN LOMBERG) 13 February 1986 (13.02.86), claims 1-7; page 2, lines 1-25 (cited in the application).	1-3,9
A	GB, A, 1 433 828 (TROMMSDORFF) 28 April 1976 (28.04.76).	1,4,7,9
A	GB, A, 2 239 020 (KALAMAZOO HOLDINGS INC.) 19 June 1991 (19.06.91), abstract; claims 13-18.	1,4-6

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 February 1993 (26.02.93)

Date of mailing of the international search report

03 March 1993 (03.03.93)

Name and mailing address of the ISA/ AT
AUSTRIAN PATENT OFFICE
Kohlmarkt 8-10
A-1014 Vienna
Facsimile No. 0222/53424/535

Authorized officer

Hauswirth e.h.

Telephone No.

0222/53424/136

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/KR 92/00083

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WD A1 8600913	13-02-86	AU A1 46368/85	25-02-86
		DE A1 3427787	30-01-86
		EP A1 190239	13-08-86
GB A 1433828	28-04-76	AT B 317250	26-08-74
		AU A1 63073/73	05-06-75
		BE A1 808464	29-03-74
		CA A1 1010854	24-05-77
		CH A 590880	31-08-77
		DE A1 2260536	04-07-74
		DE B2 2260536	05-12-74
		DE C3 2260536	10-07-75
		ES A1 421313	16-04-76
		HU P 166786	28-05-75
		JP A2 49133512	21-12-74
		NL A 7316976	13-06-74
		SE B 409461	20-08-79
		SE C 409461	29-11-79
		SU D 520906	05-07-76
		US A 3911115	07-10-75
		ZA A 7308976	27-11-74
GB A 2239020		CA AA 2028156	25-04-91
		CH A 680790	13-11-92
		DE A1 4033690	25-04-91
		DK A0 2556/90	23-10-90
		DK A 2556/90	25-04-91
		ES AA 2032360	01-02-93
		FR A1 2653439	26-04-91
		GB A0 9022988	05-12-90
		GB A1 2239020	19-06-91
		JP A2 3160946	10-07-91
		US A 5053240	01-10-91

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.